PCT/IB03/05331

IB03/05331

RLC-450

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

**GOVERNMENT OF INDIA**
**MINISTRY OF COMMERCE & INDUSTRY,**
**PATENT OFFICE, DELHI BRANCH,**
**W - 5, WEST PATEL NAGAR,**
**NEW DELHI - 110 008.**





*I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the* ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**1176/Del/2002** dated **21st November 2002.***

*Witness my hand this 12th day of January 2004.*

***(S.K. PANGASA)***
*Assistant Controller of Patents & Designs*

1176 DEL 02

FORM 1

21 NOV 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

**(See Sections 7, 54 and 135 and rule 33A)**

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **" PROCESS FOR THE PREPARATION OF NOVEL MONO N, N-DIMETHYL ACETAMIDE MONOHYDRATE SOLVATE OF LORACARBEF "**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. NEERA TEWARI

c. HASHIM NIZAR POOVANATHIL NAGOOR MEERAN

d. BISHWA PRAKASH RAI

e. SHAILENDRA KUMAR SINGH

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

**DR. B. VIJAYARAGHAVAN**
**Associate Director – Intellectual Property**
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 6343126; 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, YATENDRA KUMAR, NEERA TEWARI, HASHIM NIZAR POOVANATHIL NAGOOR MEERAN, BISHWA PRAKASH RAI, SHAILENDRA KUMAR SINGH of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(YATENDRA KUMAR)

b. Neera Tewari

(NEERA TEWARI)

c.

(HASHIM NIZAR POOVANATHIL NAGOOR MEERAN)

d. BRai

(BISHWA PRAKASH RAI)

e. Shailendra Kumar Singh

(SHAILENDRA KUMAR SINGH)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:
   a. Provisional Specification (3 copies)
   b. Drawings (3 copies)
   c. Statement and Undertaking on FORM – 3
   d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **685647** dated **05.11.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 21ST day of **NOVEMBER, 2002.**

**For Ranbaxy Laboratories Limited**

Sd/-

**(SUSHIL KUMAR PATAWARI)**
**COMPANY SECRETARY**

FORM 2

1170-DEL-02

The Patents Act, 1970
(39 of 1970)

21 NOV 2002

PROVISIONAL SPECIFICATION
( See Section 10 )

# PROCESS FOR THE PREPARATION OF NOVEL MONO N, N-DIMETHYL ACETAMIDE MONOHYDRATE SOLVATE OF LORACARBEF

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
*(A Company incorporated under the Companies Act, 1956)*

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of mono-N,N-dimethyl acetamide monohydrate solvate of loracarbef, a convenient intermediate for preparing loracarbef.

Loracarbef is a synthetic β-lactam antibiotic of the carbacephem class for oral administration. Loracarbef is disclosed by Hashimoto et al., in U.S. Patent No. 4,335,211.

Hashimoto et al has disclosed a class of 1-carbacephalosporins having desirable antibiotic and oral activity characteristics. These compounds have been evaluated for the treatment of various conditions such as common upper and lower respiratory tract infections caused by the pathogen H. influenza. One such compound, 7-(R)-phenylglycinamido-3-chloro-1-azabicyclo[4.2.0]oct-2-ene-8-one-2-carboxylic acid, known as Loracarbef, has shown activity against a broad spectrum of bacteria in laboratory tests. Loracarbef has proven to be a relatively stable compound, which exhibits high blood levels and relatively long half-life.

Loracarbef is chemically (6R,7S)-7-[(R)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-1-azabicyclo [4.2.0]oct-2-ene-carboxylic acid, monohydrate having structural formula I as shown in the accompanied drawings.

Loracarbef has been isolated in various forms, including the crystalline monohydrate form (which is the drug) disclosed in the European patent publication EP 0311,366.. Other solvate forms of the compounds known are bis (DMF), dihydrate mono(DMF) and mono (DMF) forms and are disclosed in US Patent No. 4,977,257. The crystalline dihydrate form of loracarbef is disclosed in European patent publication, EP 0369,686; crystalline anhydrate form of loracarbef disclosed in US Patent No. 5,580,977, which is converted to crystalline monohydrate having specific bulk density.

The solvates referred above are convenient intermediate for preparing loracarbef in general and to the monohydrate form of loracarbef specifically. Accordingly, methods for the total synthesis of these promising compounds and intermediates to these compounds are highly desirable, particularly methods, which are adaptable to large scale manufacture, and result in high yields and reduced cost of manufacture.

It is a well known fact that in order to formulate a bulk product it is critical that the compound intended for pharmaceutical use to have sufficient density such that the product could be

formulated for pharmaceutical use. For loracarbef monohydrate, a density of greater than or equal to 0.5 g/ml is desired in order to facilitate the formulation of the bulk product.

As per the process described in EP 0,369,686, the crystalline monohydrate form of loracarbef may be prepared by first suspending loracarbef dihydrate in water and then effecting solution by the addition of acid followed by the adjustment of the pH with base, or by the addition of base followed by acid. The resultant loracarbef may be crystallized and then isolated by filtration.

However, this process is considered commercially unattractive because it yields loracarbef monohydrate in the form of a fine, fluffy powder with a density of approximately 0.2 g/ml. This density renders the bulk product, loracarbef monohydrate, very difficult to formulate. Since this compound is intended for pharmaceutical use, the ability to formulate the bulk product is critical. For loracarbef monohydrate, a density of greater than or equal to 0.5 g/ml is desired in order to facilitate the formulation of the bulk product. Thus, it was necessary to improve the process of EP 0,369,686, in order to obtain a bulk product with a sufficient density such that the product could be formulated for pharmaceutical use.

What is needed in light of the above difficulties is a process for preparing crystalline loracarbef monohydrate with specific bulk density in a more efficient manner.

The present invention provides an efficient process for preparing loracarbef monohydrate having the desired bulk density.

The first aspect of the present invention is directed to the process of preparing mono N, N-dimethylacetamide monohydrate solvate of loracarbef having the X-ray powder diffraction pattern listed in the Table as specified in the Example 1.

Another aspect of the present invention is directed towards the facile conversion of mono N, N-dimethylacetamide monohydrate solvate of loracarbef to loracarbef monohydrate that results in a commercially desirable form of the bulk product.

Yet another aspect of the present invention is directed towards a process for preparing crystalline loracarbef monohydrate having a bulk density greater than or equal to 0.6 gm/ml.

Accordingly, the present invention provides a process for the preparation of mono-N, N-dimethylacetamide monohydrate solvate of loracarbef of structural formula II as shown in the accompanied drawings.The process compries mixing the compound of formula III wherein $R_1$ is hydrogen, trihalo ($C_1$-$C_4$ alkyl) , $C_1$-$C_4$ alkyl, $C_1$-$C_4$ substituted alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ substituted alkoxy, $C_1$-$C_6$ alkylthio, $C_1$-$C_6$ substituted alkylthio, methoxy methyl, carbamoyloxy methyl, acetoxymethyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ substituted alkenyl, or halogen such as bromo, chloro, fluoro, and iodo; $R_2$ is a carboxy-protecting group with N,N, dimethylacetamide and a cyclic amine base containing 0-1 oxygen atoms or dimethylbenzylamine, to form the free amine of the compound of formula IV and thereafter, without isolating the free amine, mixing the free amine with an acylating agent of the formula V wherein $R_3$ is an amino protecting group and L is a leaving group.

The term "carboxy-protecting group" refers to one of the ester derivatives of a carboxylic acid group which is not sterically hindered and are commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such groups are allyl, alkyl, benzyl and substituted benzyl groups, silyl group and halo-substituted alkyl groups such as the 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, and 2-iodoethyl groups. Further examples of these groups are found in E. Haslam, "Protective Groups in organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 5. A preferred ester group is the 4-nitrobenzyl group.

The term "amino-protecting group" refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound.

The amino protecting group $R_3$ of Formula V is selected from either the carbamates such as t-butoxycarbonyl or benzyloxycarbonyl, or the enamines. Preferred amino-protecting groups are the t-butoxycarbonyl, phenoxyacetyl, and enamines derived from ($C_1$-$C_4$ alkyl)acetoacetate groups. Similar amino-protecting groups used in the cephalosporin, penicillin and peptide art are also embraced by the above terms. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 2, and T. W. Greene, "Protective Groups in organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 7.

The term "leaving group" means a leaving group which, under the reaction conditions will leave, allowing the free amine to bond to the carbonyl group. Leaving groups include those where L is of the formula VI where $R_4$ is $C_1$-$C_6$ alkyl, or L is Cl, Br, I, active esters such as p-nitrophenyl; the adducts of dicyclohexylcarbodiimide.

The base used is selected from the group consisting of 5 or 6 membered tertiary cyclic amines which may contain an oxygen atom, or dimethylbenzylamine. Preferable tertiary cyclic amine bases are N-methylmorpholine (NMM) and N-methylpiperidine (NMP). The base is preferably in an amount of between about 1 to 1.3 molar equivalents, and most preferably at about 1.13 molar equivalents. Preferably N-methylmorpholine (NMM) is used.

The hydrochloride salt of formula III is prepared by the process described in the European Patent Application 0266896.

In forming the free amine (IV) a sufficient amount of base is added to the hydrochloride salt to neutralize the compound and form the free amine. In the preferred method for producing the free amine, the hydrochloride salt (III) is neutralized by adding it to a stirred mixture of N, N- DMAc of such a volume that the final solution will be about 0.5M, and between about 1 to 1.3 equivalents of N-methyl morpholine (NMM), at ambient temperature. The mixing initially occurs at room temperature (20°C) for a time between about 10-20 minutes, and then it is cooled to a temperature of between about -5 to -10°C.

The mixed anhydride of formula V is prepared by adding about 1.2 equivalents of the Dane salt of phenylglycine of Formula VII (which may be prepared according to the procedure of Dane et al., Angew. Chem., Vol. 74, 873 (1962), with a volume of N, N- DMAc sufficient to result in a concentration of about 0.25M, and stirring the mixture at ambient temperature for 20-60 minutes. The mixture is then cooled to -20 to -10°C and N- methylmorpholine (NMM) (0.025 equivalents) and methanesulfonic acid (0.05 equivalent) are added. Ethyl chloroformate (1.17 equivalent) is then added and the mixture stirred for 1 to 2 hours, thus resulting in the mixed anhydride (V).

The amino- and carboxy-protecting groups are removed by methods well known in the art. Examples of conditions for the removal of these two types of protecting groups can be found in standard works on the subject, such as E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapters 2 and 5; and T. W. Greene,

"Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981, Chapters 5 and 7, respectively.

The acylation method in the present invention comprises adding the cooled free amine mixture (IV) to the mixed anhydride (VIII) over a period of 10-20 minutes, while keeping the internal reaction temperature between –5° and -15°. The reaction is stirred at same temperature until the acylation reaction is substantially complete (as determined by conventional means such as thin layer chromatography, HPLC).

The mixture is then warmed slowly to approximately 0°C and the reagents for removing the amino and carboxy protecting groups (such as water, concentrated hydrochloric acid, and zinc dust for the pNB ester) are added slowly while maintaining the initial temperature of the solution.

For deprotecting the protected amino and protected carboxy group, a mixture of concentrated HCl in water (2:1) at a temperature at 0° to -10°C, is added to the acylation solution (III) over a 30-45 minutes period, during which the reaction temperature is kept below 0°C. Zinc dust (3.5 equivalents) is then added over 50-70 minutes, keeping the temperature at below 0°C. Approximately 1.2 equivalents of HCl is added and the reaction mixture warmed to ambient temperature over a 45-60 minute period. The mixture is stirred for 5-6 hours at ambient temperature and semi-carbazide hydrochloride (1.15 equivalents) is added, followed by 30-60 minutes of stirring. The pH is adjusted to 2.9-3.1 with 28% aqueous ammonia and the mixture is filtered through a hyflo pad. The filtrate is warmed to 48-55°C and is adjusted to a pH of 4.8 to 5.0 using 28% aqueous ammonia. Solid separates from the solution and the reaction mixture is stirred for 30 minutes, and the pH is continuously adjusted to 5.8-6.2. The temperature of the mixture is lowered to 20-25°C and added a polar solvent such as acetone to it and stirred for another 30 minutes before being filtered.. The crystals are collected by filtration, washed with acetone, cooled to 20 –25°C, and dried to give the mono N, N-dimethylacetamide monohydrate solvate of loracarbef.

The process disclosed results in high yields of compounds of formula II yields, (> 90%).

It will be understood that the listing for substituents is exemplary and not exhaustive, and equivalents are expected to be encompassed by the spirit of the invention.

As mentioned above, mono N, N-dimethylacetamide monohydrate solvate of loracarbef is useful as an intermediate to loracarbef monohydrate. Surprisingly, the loracarbef monohydrate prepared from the mono N, N-dimethylacetamide monohydrate solvate of loracarbef is found to have a bulk density equal to or greater than 0.6 g/ml.

The monohydrate is prepared suspending mono N, N-dimethylacetamide monohydrate solvate of loracarbef in water. The most common procedure is to effect solution of the starting material by the addition of a minimum amount of acid, generally 6N (or more dilute) hydrochloric acid. Temperature of the solution is raised to about 50° C and slowly add 28% ammonia solution to the solution until a pH of approximately 4.8 is obtained. The gradually developing suspension is stirred and maintained at about 50° C. during the addition of the base. The warm pH-adjusted suspension (50° C.) is cooled to approximately 20° C, stirred, filtered (such as on Buchner funnel) and the collected solid dried at 40-45° C to yield crystalline loracarbef monohydrate having bulk density equal to or greater than 0.6g/ml.

In the following section preferred embodiments are described by a way of example to illustrate the process of the invention. However, these are not intended in any way to limit the scope of the claims.

In the following Example, the terms theN, N-dimethylacetamide monohydrate solvate of loracarbef, nuclear magnetic resonance spectra, mass spectrum and infrared spectroscopy are abbreviated N,N-DMAc, NMR, MS and IR, respectively.
In conjunction with the NMR spectra, the following abbreviations are used: "s" is singlet, "d" is doublet, "t" is triplet, "q" is quartet, and "m" is multiplet.

The NMR spectra were obtained on a Bruker (DRX 300) 300 MHz instrument. The chemical shifts are expressed in ppm values (parts per million downfield from tetramethylsilane).

**EXAMPLE 1**

Step A :

Preparation of N-methylmorpholine salt

To a mixture of N, N-dimethylacetamide (60 ml) and N-methylmorpholine (3.0 g), added p-nitrobenzyl 7 β-amino-3-chloro-1-carba (1-dethia)-3-cephem-4-carboxylic acid hydrochloride

(10.0 g) in portions at 20-25°C to form the free amine. The reaction mixture was stirred for 30 minutes and then cooled to -5 to -10°C.

Step B :

Preparation of mixed anhydride

The Na/K Dane salt of phenylglycine (VII) (9.3 g) was suspended in N, N-dimethylacetamide (150ml) and stirred for 30-40 minutes. The reaction mixture was coolled to –20 – 15°C and added methane sulphonic acid (0.12 g) and N-methylmorpholine (0.06 g) to it. Ethylchloroformate (3.3 g) was further added in one portion and stirring was continued for 90 minutes. at –10 to -15°C.

Step C :

Condensation :

N-methylmorpholine hydrochloride solution containing the free amine obtained from Step A was slowly added to the mixed anhydride obtained from Step B at –20 to -10°C. The reaction mixture was stirred for 2.0 hours and monitored the progress of the reaction via T.L.C. or HPLC. After completion of the reaction, added a mixture of conc. HCl in $H_2O$ (28 ml in 14 ml $H_2O$) over a 10-15 minutes period to diprotected loracarbef followed by adding zinc powder (6.0g) which was added slowly maintaining the temperature less than +5°C. The temperature was raised to 20-25°C and stirred the reaction mixture for about 2 hours. Semicarbazide hydrochloride (3.3 g) was added and the stirring was continued for 30-35 minutes. The pH of the reaction mixture was adjusted to 2.9 to 3.0 with 28%. $NH_3$ solution and then filtered it. The filterate was warmed to about 48-55°C. and adjusted the pH to 4.8 to 5.0 solid was separated from the solution, stirred the mixture for 30 minutes and finally adjusted the pH 5.8 to 6.2. The reaction mixture was cooled to 20-25°C, added acetone, and stirred for another 30 minutes. It was then filtered and washed with acetone. The solid was dried under vacuum to give mono N,N-DMAc monohydrate solvate of loracarbef which was characterized on the basis of the data given below at 40-42°C.

Dry weight 9.0g.

Yield w/w 0.90.

NMR ($D_2O$-DCl) (300 MHz): 7.44-7.45 (s, 5H, ArH), 5.35 (d, 1H-β-lactam) 5.2 (s,1H, CH-Ph), 3.93-(m,1H-β-lactam) 2.91-3.03 (s,s, 6H, $N(CH_3)_2$) 2.55 (m, 2H, $CH_2$) 2.05 (s, 3H, $COCH_3$) 1.63 (m, 1H, CH) 1.31 (m, 1H, CH)

Moisture content (by KF) = 3.0%

IR (KBr disc) = 2980 – 3660 (s, and broad) 1780, 1700, 1630, 1580, 1460, 1400, 1390, 1380, (m to strong)

X-Ray Powder Diffraction obtained on a Rigaku (RINT 2000) instrument with nickel-filtered copper radiation (Cu:Ni) of wavelength lambda.=1.5406 Angstrom. The interplanar spacings are in the column marked "d" and are in Angstroms and the relative intensities are in the column marked "$I/I_1$ ".

| D | I/Io |
|---|---|
| 15.6 | 17.0 |
| 11.80 | 100 |
| 11.12 | 41 |
| 7.43 | 25 |
| 5.91 | 12 |
| 5.19 | 14 |
| 4.88 | 16 |
| 4.76 | 22 |
| 4.69 | 17 |
| 4.45 | 13 |
| 4.28 | 13 |
| 3.93 | 70 |
| 3.639 | 28 |
| 3.33 | 18 |
| 3.177 | 71 |
| 2.949 | 18 |
| 2.729 | 13 |
| 2.6122 | 13 |

## EXAMPLE 2

Preparation of loracarbef monohydrate from mono N, N-DMAc monohydrate solvate

Loracarbef mono N, N-dimethylacetamide monohydrate solvate (10.0 g) was suspended in water (80 ml). 12N hydrochloric acid (1.0 ml) was added to obtain a clear solution. Added activated carbon (1.0 g) and stirred the reaction mixture for 30-40 minutes. The suspension was then filtered and washed with water (30 ml). Temperature of the filterate was raised to 50-55°C and slowly adjusted the pH 1.8 – 1.9 with 8% $NH_3$ solution. The reaction mixture was stirred for 30 minutes at 50-55°C. Stirring continued for additional 30 minutes and then slowly cool to 20-25°C. The slurry was washed with water. The cake was dried in air oven at 40-45°C to yield crystalline loracarbef monohydrate (5.0 g) having bulk density greater than 0.6 g/ml.

IR, NMR and X-Ray diffraction pattern of the crystalline loracarbef monohydrate matches with the authentic samples of crystalline loracarbef monohydrate.

Dated this 21ST day of **November, 2002.**

**For Ranbaxy Laboratories Limited**

**(Sushil Kumar Patawari)**
**Company Secretary**

## ABSTRACT

This patent application relates to a novel process for the preparation of an intermediate, mono-N,N-dimethyl acetamide monohydrate solvate of loracarbef.

Ranbaxy Laboratories Limited

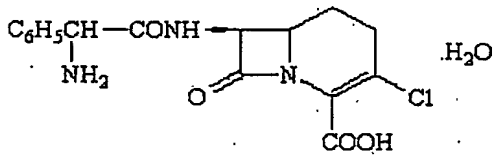
Application No.

No. of sheets = 09

Sheet 01 of 09

1176 DEL 02

21 NOV 2002



FORMULA - I

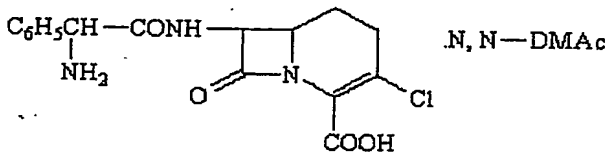
DUPLICATE

**For Ranbaxy Laboratories Limited**

**(Sushil Kumar Patawari)**
**Company Secretary**

1176 DEL 02

21 NOV 2002




FORMULA - II

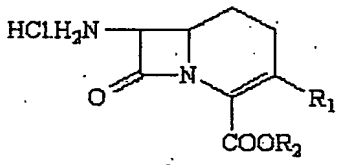
DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1176-DEL-02

21 NOV 2002




FORMULA - III

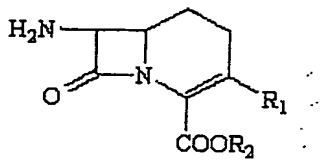
DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1178-DEL-02

21 NOV 2002




FORMULA - IV

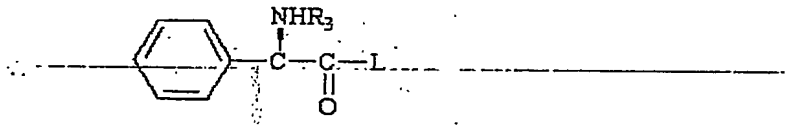
DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1176-DEL-02

21 NOV 2002




FORMULA V

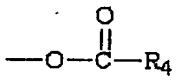


For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1176 DEL 02

21 NOV 2002



FORMULA VI

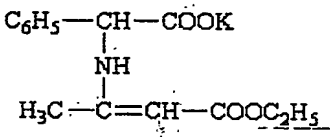
DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1173-DEL-02

21 NOV 2002



FORMULA VII

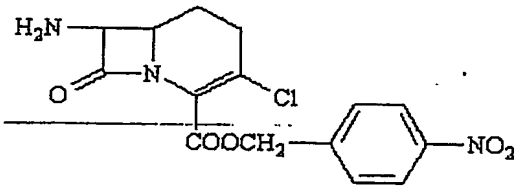
DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1176-DEL-02

21 NOV 2002




FORMULA - VIII

DUPLICATE

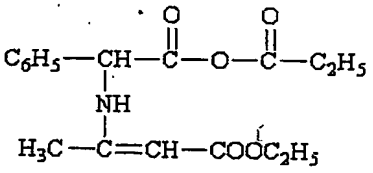
For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1173-DEL-02

21 NOV 2002

DUPLICATE



FORMULA IX

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

DOX

**Destination:**

# GVA

**Waybill:** 8802975274

**Acct: 781323929**
**Date: 01/22/2004**

**Ref:** RLL-298, -301, -316, -319, 450

REC'D 2 6 JAN 2004
WIPO PCT RO/IB

**Customs Value:** NVD

**Weight:** XD

**Origin: TTN**
**Pcs: 1**

**FR:** Ranbaxy Pharmaceuticals Inc.
Christine Kenedy
600 College Road East
Suite 2100
Princeton, NJ
08540 United States Of America
Ph: (609) 720-5622 Fax: (609)514-9779

**Description:** Legal documents

**TO: Int'l Bureau of WIPO**
**Jean-Luc Baron**
**PCT Receiving Office**
**34, chemin des Colombettes**
**Geneva**
**1211 Switzerland**
**Ph:** 41 22 338 9352 **Fax:** 41 22 910 0610

*Fold here. Affix to package using DHL plastic pouch.*

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I/we have agreed that DHL's standard terms apply to this shipment and limit DHL's liability for loss or damage to US $ 100. The Warsaw Convention may also apply (see above). I/we understand that shipment value protection is available on request, for an extra charge. I/we agree to pay all charges if the recipient or third party does not pay. I/we understand that DHL DOES NOT TRANSPORT CASH.

**SIGNATURE:** Christine Kenedy

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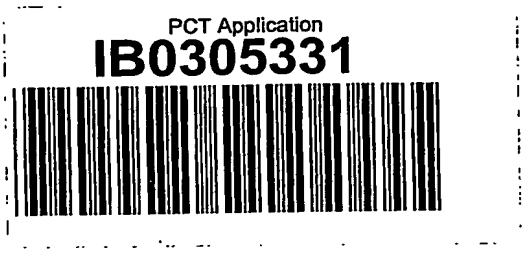
PCT Application
IB0305331